Lights, Chemicals, Action at New Lab for Phototoxicology

In the delta of southeastern Arkansas, at the National Center for Toxicological Research in Jefferson, two large laboratory rooms are bright with sunlight—not the kind that streams in through windows, but simulated solar energy from tiny lamps using an electromagnetic radiation source that closely mimics the spectrum of sunlight.

There, in the heart of the new Phototoxicology Research and Testing Laboratory, hairless mice are coated with creams similar to ones used daily by millions of people in search of a more "youthful" appearance. The question that scientists want to answer is whether the natural acids now found in almost every skin care cream on the market may actually promote skin cancer. Researchers are concerned that these acids, known as alpha- and beta-hydroxy acids, might peel away layers of the skin to the point where sunlight can damage DNA in cells at the skin's deepest levels.

Setting Sights on the Sun

Two years ago, the Center for Food Safety and Applied Nutrition, one of the five regulatory centers of the Food and Drug Administration (FDA), nominated alpha- and beta-hydroxy acids for testing of their carcinogenic potential by the National Toxicology Program. The agency's reasoning included the fact that the substances—components of skin care products—are used by millions of people (mostly women) but have never been thoroughly studied. Use of these so-called chemoexfoliants results in changes in the skin's outer layers (the stratum corneum) and epidermal tissues. According to the FDA, two consequences of using creams containing these acids are increased proliferation of epidermal epithelial cells and deeper penetration of electromagnetic radiation into the skin, both of which raise the possibility of an increased risk of skin cancer with continued use. Says Paul C. Howard, director of the phototoxicology laboratory, "Vanity may have a price."

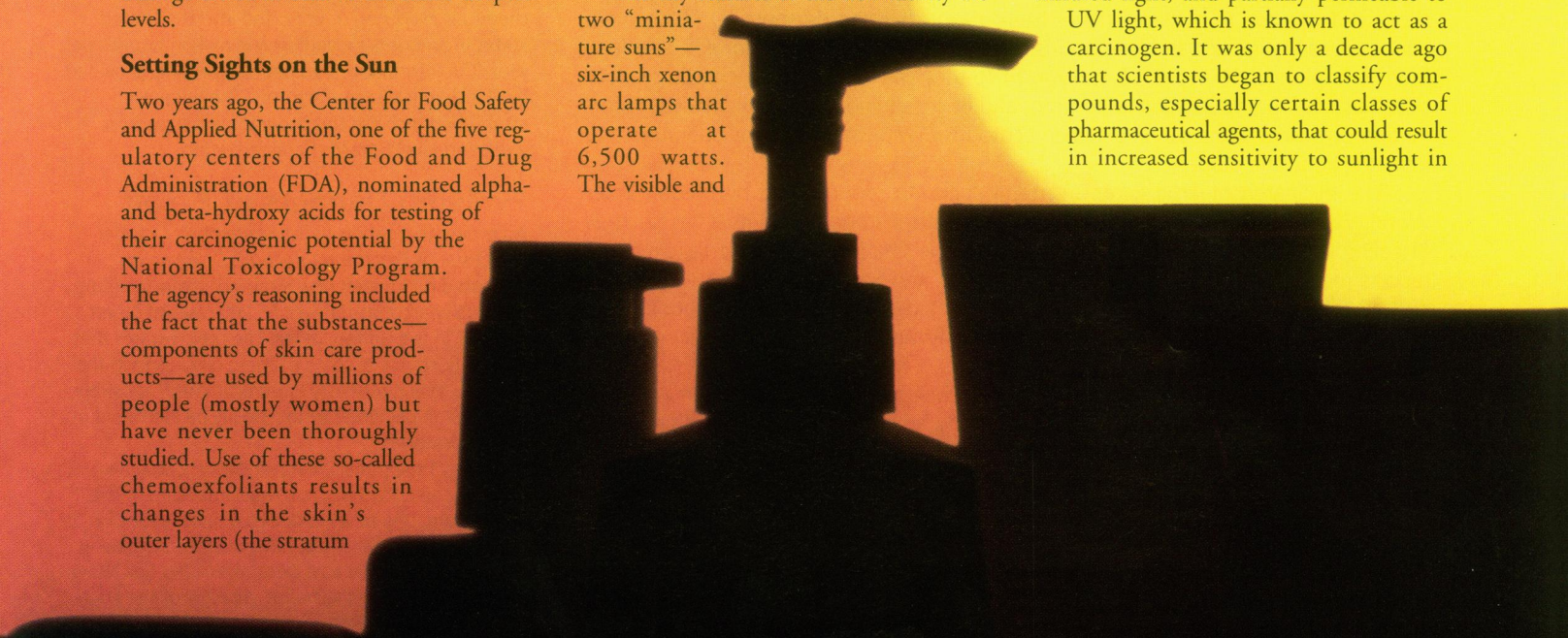
"It became apparent after surveying the literature and consulting with colleagues that in order to understand the carcinogenic potential of the alpha- and beta-hydroxy acids, studies would have to be designed to determine the effects of these acids on ultraviolet (UV) light–induced skin cancer in mice," says Howard. The FDA and the NIEHS joined together to fund a facility that would allow the simultaneous exposure of the large numbers of mice required for such studies, as well as future studies on compounds that may affect skin cancer rates.

The key features of the new facility are two "miniature suns"—six-inch xenon arc lamps that operate at 6,500 watts. The visible and UV radiation emitted from each lamp, when filtered through glass designed to simulate the earth's atmosphere, closely mimics the spectrum of solar light. Researchers at the laboratory can expose about 5,000 mice a day to the simulated solar light. Although, says Howard, sunlight can be simulated on a small scale (dozens of mice per day) with equipment found in university laboratories, carcinogenicity studies can be large and are very difficult to do. "The numbers of animals required for a carcinogenicity study required this type of facility," he says.

The laboratory was launched through an interagency agreement established in 1992 between the NIEHS and the FDA. Other projects currently funded under this agreement include toxicological assessment of the pediatric anesthetic chloral hydrate, the fungal toxin fumonisin B_1, the aquatic fungicide malachite green, the liquor and wine fermentation products urethane and ethanol, and a number of endocrine-disrupting chemicals.

The Acid Test for Skin

The skin is the largest organ of the human body and is highly permeable to visible and infrared light, and partially permeable to UV light, which is known to act as a carcinogen. It was only a decade ago that scientists began to classify compounds, especially certain classes of pharmaceutical agents, that could result in increased sensitivity to sunlight in



someone exposed to them, says Donald Forbes, a researcher at Argus Laboratories in Horsham, Pennsylvania, and an adviser to the National Toxicology Program on the development of the phototoxicology laboratory. In the 1980s, Forbes and fellow dermatologists at Temple University in Philadelphia launched the first phototoxicity tests using simulated sunlight when they tested retinoic acid (Retin-A). Retin-A turned out to be a weak tumor promoter, but Forbes later found that drugs used to treat psoriasis and a new class of very effective oral antibiotics, the fluoroquinolones, produce serious sunburns and rashes in patients. "Drugs like these may be taken internally," says Forbes, "but they flow through the blood to the skin and make living cells at the base of the epidermis much more sensitive to DNA damage."

FDA/NIEHS Phototoxicology Research and Testing Laboratory

Soaking in the sun for science's sake. Researchers at a new NTP phototoxicology laboratory are using lamps that simulate sunlight to test for effects of exposures to sun and chemoexfoliants on mice. The results may indicate whether the combination of UV radiation and certain components of beauty products may actually promote skin cancer in humans.

Researchers believe that altering the structure of the skin using creams containing alpha- and beta-hydroxy acids could alter the transmission of some wavelengths of light through the skin. In addition, says Howard, "The skin hates acid. It's buffered to maintain a pH that provides a suitable environment for keratocytes, the predominant skin cell." While natural alpha-hydroxy acids such as those found in fruit are absorbed nicely in the acid-rich environment of the stomach, Howard points out that "we don't normally rub fruit on our skin." There are published data, he says, showing that individuals treated with chemoexfoliants are more susceptible to sunburns. The question, he says, is whether the use of these acids causes a change in skin cancer rates, and if so, whether glycolic acid (an alpha-hydroxy acid) and salicylic acid (the most widely used beta-hydroxy acid) work differently.

It is hoped that the phototoxicology laboratory will answer these questions and others as well. According to John Bucher, project officer for the NIEHS interagency agreement with the FDA, the laboratory is designed for testing not only cosmetic chemicals but also other potentially photoactive drugs and environmental agents for UV radiation– or simulated solar light–induced toxicity and cancer. For example, foods such as celery and herbal remedies such as St. John's wort both contain chemicals that react to sunlight, and may be studied in the future. Says Bucher, "We have an obligation to look at natural substances as well as environmental synthetic chemicals that might be phototoxic, and this center will help us do that." **–Renée Twombly**